Biologics and Biosimilars

Biologics and Biosimilars — Regulatory Requirements Impacting EHRs and Pharmacy Systems Used by IDNs

Speaker Introduction

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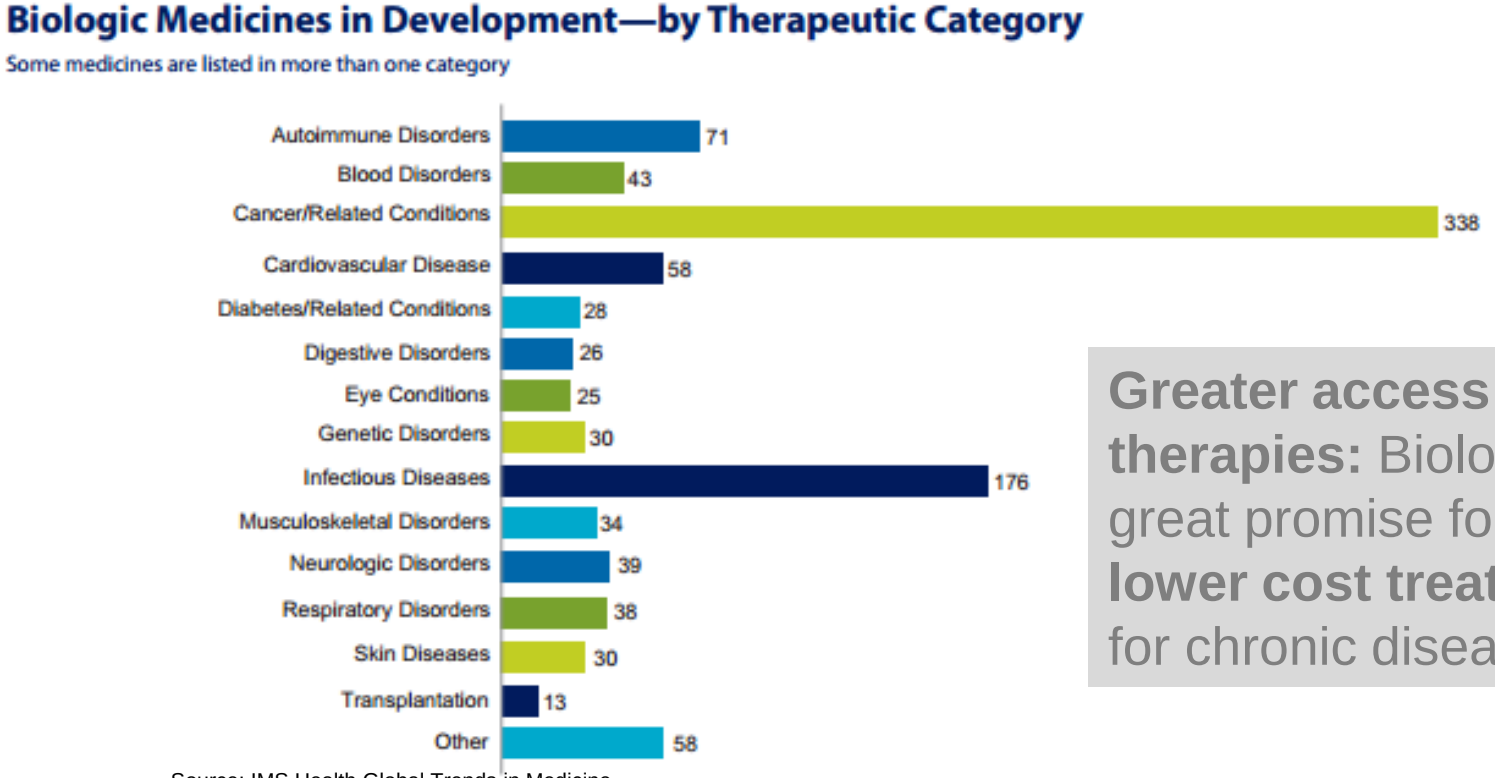
Agenda

- Biologics and Biosimilars: An Overview
- Current FDA Activity around Biologics and Biosimilars
- State Regulatory Activity – Biologic and Biosimilar Substitution Communication
  - Components of Legislation
  - Standardization efforts for electronic communication
- Impact of Regulatory Activity on IDNs, EHR Vendors and Pharmacy System Vendors
- Recommendations for EHRs and pharmacy systems
- Describe best practices by IDNs to capture and support specific product identification, ensure precise product tracking within their EHRs and allow for accurate, efficient reporting and tracing of adverse events associated with biologics

Why Are Biologics so Important?

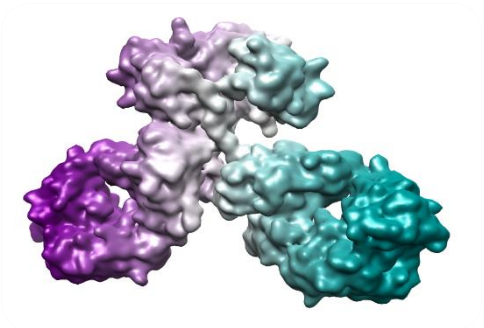


Source: IMS Health Global Trends in Medicine.

Greater access to therapies: Biologics hold great promise for providing a **lower cost treatment option** for chronic diseases

What is a Biologic Medicine?

- A biologic is a substance that is made from a living organism or its products.[1]
- Biologics are developed in living systems, including bacterial[2], yeast[3,4], and mammalian[5,6] cells.

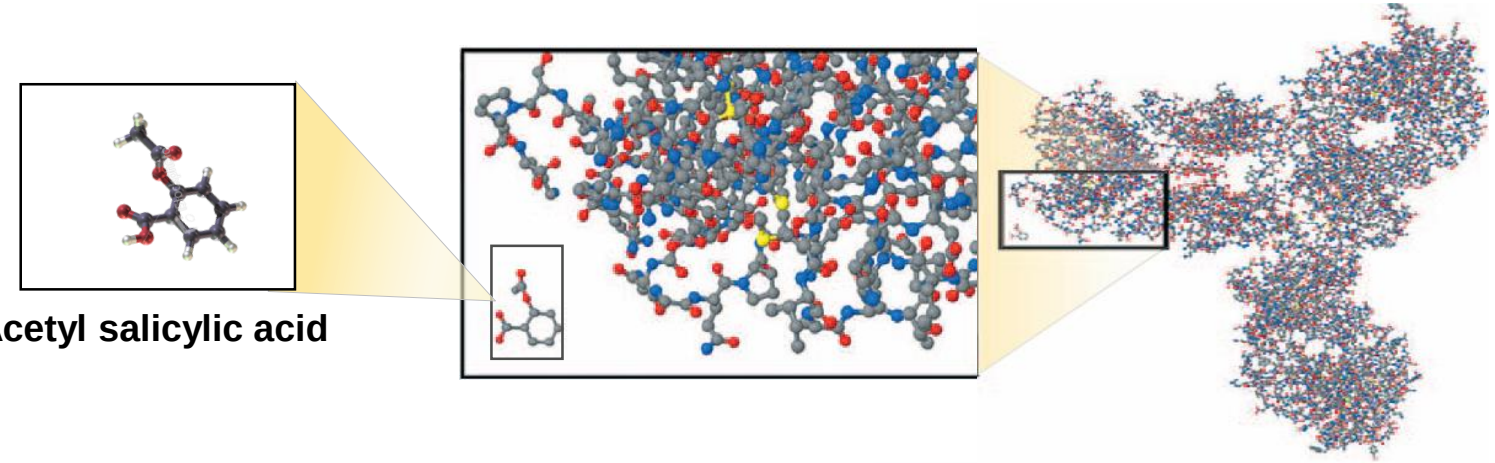


1. National Cancer Institute: Dictionary of Cancer Terms. Available at: http://www.cancer.gov/dictionary?cdrid=426407. Accessed January, 18, 2013.
2. Baneyx F, *Curr Opin Biotechnol*. 1999;10:411-421. 3. Cregg JM, et al. *Mol Biotechnol*. 2000;16:23-52. 4. Malys N, et al. *Methods in Enzymology*. 2011;500:197-212. 5. Lackner A, et al. *Anal Biochem*. 2008;380:146-148. 6. Rosser MP, et al. *Protein Expr Purif*. 2005;40:237-243.

Biologics are Larger and Structurally More Complex than Small Molecule Drugs

Small molecules (chemically based drugs)[1]

Biologics (protein-based drugs)[1]



Acetyl salicylic acid

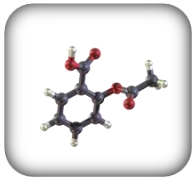
Example

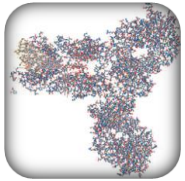
Acetyl salicylic acid[2]
21 atoms
MW = 180 Da

Biologic (monoclonal antibody)[3]
~ 25,000 atoms
MW = ~ 150,000 Da

1. Kozlowski S, et al. *N Engl J Med.* 2011;365:385-388.
2. Acetyl salicylic acid comprehensive prescribing information; www.fda.gov/ohrms/dockets/ac/03/briefing/4012B1_03_Appd%201Professional%20Labeling.pdf. Accessed January 24, 2013;
3. Davies DR, et al. *Ann Rev Biochem*. 1975;44:639-667.

Differences Between Small Molecules and Biologics





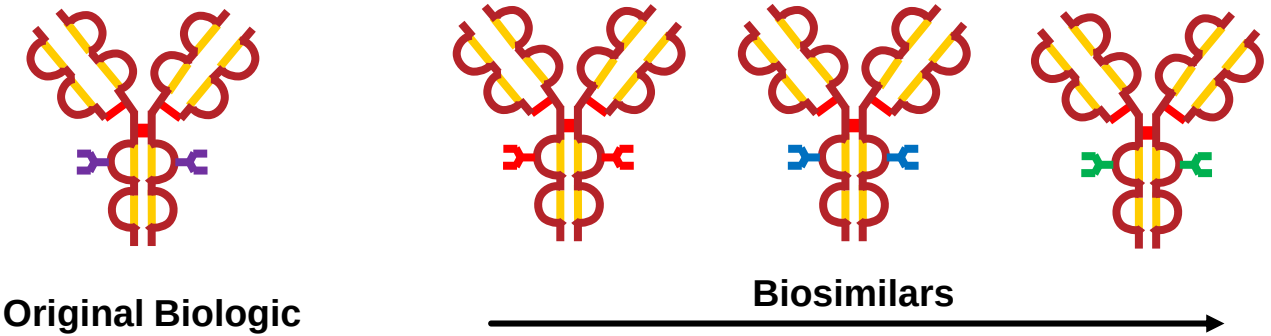
Properties	Small Molecules	Biologics
Example	Acetyl salicylic acid[1] 29 atoms; MW = 180 Da	Biologic - monoclonal antibody ~25,000 atoms; MW = ~ 150,000 Da[6]
Size	Small[2]	Large[2] – ~600x larger
Structure	Simple[3] and well defined[2,4]	Complex with many options for post-translational modification[7]
Manufacturing	Predictable chemical process; Identical copy can be made[2]	Each manufactured in a unique living cell line[2] Similar but not identical copy can be made[2]
Characterizations	Easy to fully characterize[5]	Difficult to characterize fully due to a mixture of related molecules[2]
Stability	Relatively stable[2]	Sensitive to storage and handling conditions[2]
Immunogenicity	Lower potential[2]	Higher potential[2]

Images are for illustrative purposes and are not to scale.

1. Acetyl salicylic acid comprehensive prescribing information.www.fda.gov/ohrms/dockets/ac/03/briefing/4012B1_03_Appd%201Professional%20Labeling.pdf.
Accessed January 24, 2013; **; 2. Genazzani AA, et al. *Biodrugs*. 2007;21:351-356; 3. Prugnaud JL. *Br J Clin Pharmacol*. 2007;65:619-620; 4. Crommelin DJ, Storm G, Verrijk R, et al. *Int J Pharm*. 2003;266:3-16; 5. Gottlieb S. *Am J Health Syst Pharm*. 2008;65(suppl 6):S2-S8; 6. Davies DR, et al. *Ann Rev Biochem*. 1975;44:639-667;
7. Roger SD. *Nephrology*. 2006;11:341-346.**

What are Biosimilars?

- Biosimilars are highly similar, but not identical to, existing biological products.[1]
- The Public Health Service Act defines biosimilar or biosimilarity as:
  - "the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components,"[2] and
  - "there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product."[2]



1. Mellstedt H, et al. *Ann Oncol.* 2008;19:411-419.
2. Section 7002(b)(3) of the Affordable Care Act, adding section 351(i)(2) of the Public Health Service Act.

FDA Perspective: A "Totality of the Evidence" Approach will be Applied to Assess Biosimilarity

Generics

- Establish same active ingredient
- Demonstration of bioequivalence

Biosimilars

- Extensive structural and functional characterization
- Consider need for animal data to assess toxicity
- Clinical studies to compare PK/PD, safety/efficacy, and immunogenicity

→

- Sufficient to demonstrate that the product is "highly similar" to the reference product and safe, pure, and potent for one or more approved conditions of use
- FDA has discretion to determine that certain studies not required

Food and Drug Administration. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf. Accessed September 13, 2016.

Biosimilar Interchangeability Designation Requires Evidence Beyond That Needed to Demonstrate Biosimilarity

Biosimilarity

- **Highly similar** notwithstanding minor differences in clinically inactive components
- No clinically meaningful differences in **safety, purity, and potency**

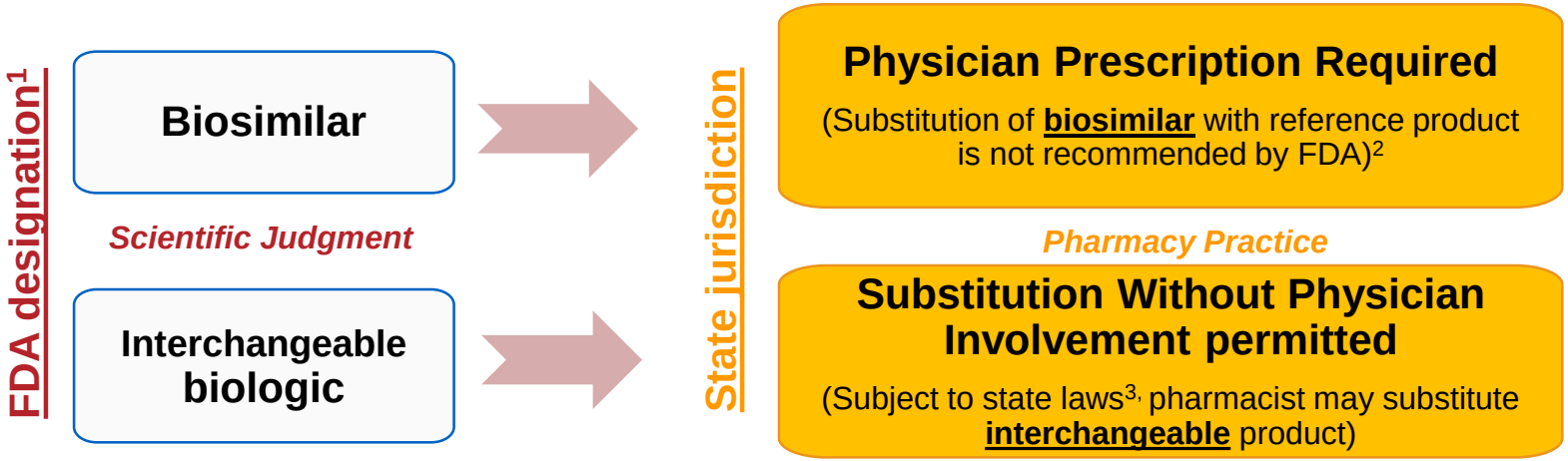
Interchangeability

Approved as a biosimilar **AND**:

- Expectation of **same clinical result** in any given patient and…
- For a product that is administered more than once, **no additional risk to safety or efficacy** as a result of alternating or switching

Patient Protection and Affordable Care Act. http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=111_cong_bills&docid=f:h3590pp.txt.pdf http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/ucm241720.htm. **Last accessed September 13, 2016.**

FDA Determines Biosimilar Interchangeability, While Automatic Substitution Is Governed by States



- FDA policy on approval standards for biosimilars does not address automatic substitution
- There is ongoing legislative activity in multiple states with regard to automatic substitution of interchangeable biologics for the reference product[3]

1. Patient Protection and Affordable Care Act. 2009. http://www.gpo.gov/fdsys/pkg/BILLS-111hr3590pp/pdf/BILLS-111hr3590pp.pdf. Accessed April 30, 2015.
2. FDA. http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/ucm241718.htm. Accessed February 18, 2015.
3. NCSL. *State Laws and Legislation Related to Biologic Medications and Substitution of Biosimilars.* 2014. http://www.ncsl.org/documents/health/Biologics_BiosimilarsNCSLReport_July_2014.pdf. Accessed April 4, 2015.

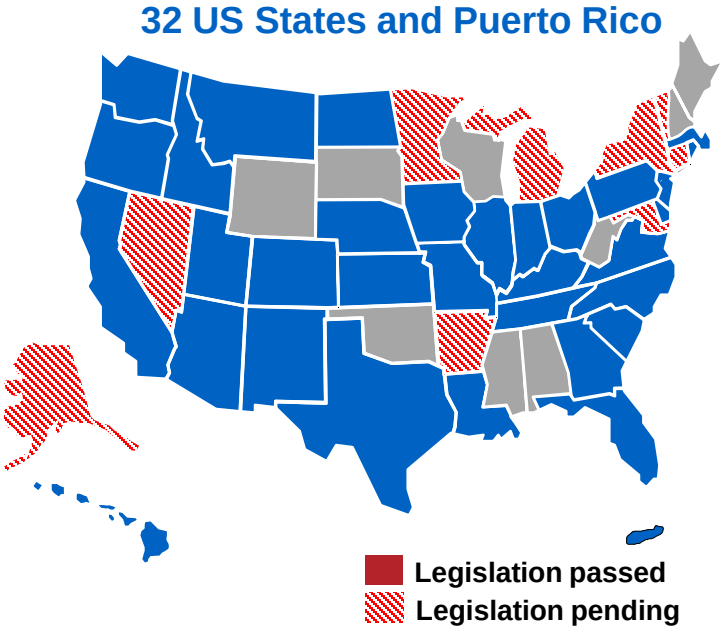
BREAKING: 1/17/2017 FDA Issued Draft Guidance on Demonstrating Biosimilar Interchangeability

Summary of guidance:

- Biosimilarity requirements are met first
- Totality of evidence will be considered
- Data and information showing product can be expected to produce the same clinical result as the RP* in ALL of the RP's licensed conditions of use expected
- Seeking licensure for ALL RP's licensed conditions of use recommended
- Extrapolation is acceptable when justified
- Switching studies generally expected
- Presentation/s generally limited to those of the RP
- Post marketing safety monitoring may be required but is itself not sufficient

* RP = Reference Product

32 States Have Enacted Laws Related to Interchangeable Biosimilar Substitution and Biologics Tracking



- Indiana
- Delaware
- Massachusetts
- North Dakota
- Florida
- Virginia
- Oregon
- California
- Colorado
- Illinois
- Idaho
- Louisiana
- New Jersey
- North Carolina
- Tennessee
- Texas
- Utah
- Kentucky
- Arizona
- Missouri
- Rhode Island
- Hawaii
- Pennsylvania
- Washington
- Georgia
- Puerto Rico
- Ohio
- Montana
- Iowa
- New Mexico
- Kansas
- South Carolina
- Nebraska

http://www.ncsl.org/research/health/state-laws-and-legislation-related-to-biologic-medications-and-substitution-of-biosimilars.aspx. **Last updated Mar. 31, 2017.**

Key Provisions of State Biosimilar Legislation

Principle	Prevailing Generic Requirements	Suggested Biosimilar Requirements
Substitution based on an FDA determination	Yes-therapeutic equivalence	Yes-interchangeable
The prescribing physician should be able to specify ‘dispense as written’	Yes	Yes
The patient should be informed of the substitution	Yes	Yes
Pharmacy records should be maintained	Yes	Yes
Only after dispensing, the patient’s medical record should be updated with HCP (e.g., through direct entry into a shared electronic record, communication via fax)	No	Yes

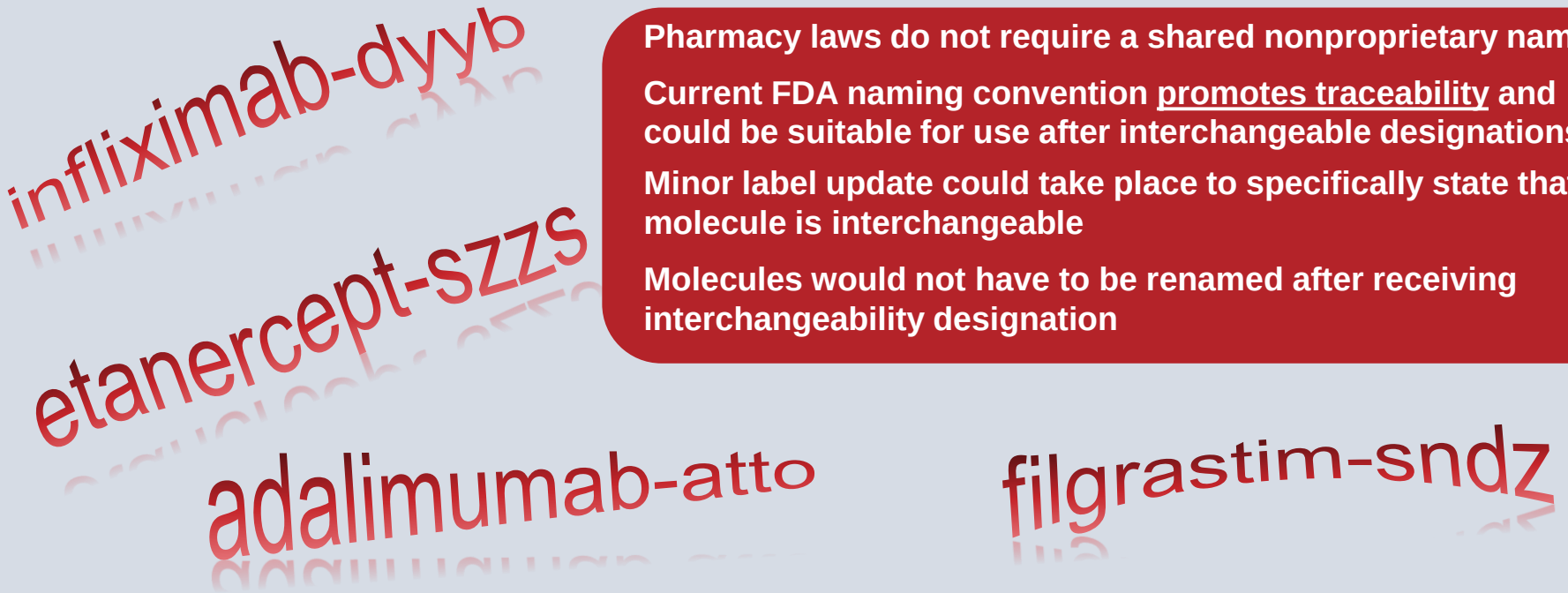
Sample State Legislative/Regulatory Language

- **FDA Certified Interchangeability**
  - Arizona: "Allows a pharmacist to substitute a biological product **if the FDA has determined that the biological product is interchangeable** with the prescribed biological product"
- **Electronic Communication**
  - Idaho: "Communication shall occur via an entry in an interoperable electronic medical records system, an electronic prescribing technology, a pharmacy benefit management system or a pharmacy record **that can be accessed electronically by the prescriber.**"
- **Patient Notification**
  - Florida: "The pharmacist **must notify the patient or person at the counter of the substitution"**
- **Prescriber's "Brand Medically Necessary" Blocks Substitution**
  - California: "Authorizes a pharmacist to select an alternative biological product when filling a prescription order for a prescribed biological product if the alternative biological product is designated interchangeable by the FDA **and the prescriber does not personally indicate that a substitution is not to be made."**

Sample State Legislative/Regulatory Language

- **Pharmacy Records Must Be Retained**
  - Delaware: "Maintain a three year record of such substitutions"
- **Posted List of Interchangeables**
  - Hawaii: "Requires pharmacists to inform consumers of **interchangeable biological products from the Hawaii list** when filling a prescription order and to communicate the product name and manufacturer to the practitioner after dispensing the product."
- **Price Related Provisions**
  - Georgia: "Pharmacist shall dispense the **lowest retail priced interchangeable biological product which in in stock"**
  - Arizona: "Requirement that the **pharmacy notify the patient of any price difference."**
- **Other Provisions**
  - Delaware: "Provide **liability protections** for pharmacists who substitute biosimilars."
  - Missouri: "Requires notification to patients and within 5 days communicate with prescriber"

Biologics Will Be Named Differently



- Pharmacy laws do not require a shared nonproprietary name
- Current FDA naming convention promotes traceability and could be suitable for use after interchangeable designations
- Minor label update could take place to specifically state that a molecule is interchangeable
- Molecules would not have to be renamed after receiving interchangeability designation

Interchangeable biosimilars - maintain unique, manufacturer specific suffixes

FDA. *Nonproprietary Naming of Biological Products. Guidance for Industry.* Published Jan 2017.

The EHR market continues to expand as most HCPs have integrated the technology into their practices

EHR systems are becoming the digital platforms where doctors practice: **>85% of physicians are ePrescribing** and **>80% of office-based physicians are using EHRs**

HCPs spend an average of **3.3 hours per day using EHR systems**, twice as long as on all other digital resources combined

Opportunities exist to integrate utilization management tools within EHRs and ePrescribing workflow for **both specialty and non-specialty medications**

References: CMI Media; Decision Resource Group; GHG

Impact of Naming Convention and Interchangeability Indication

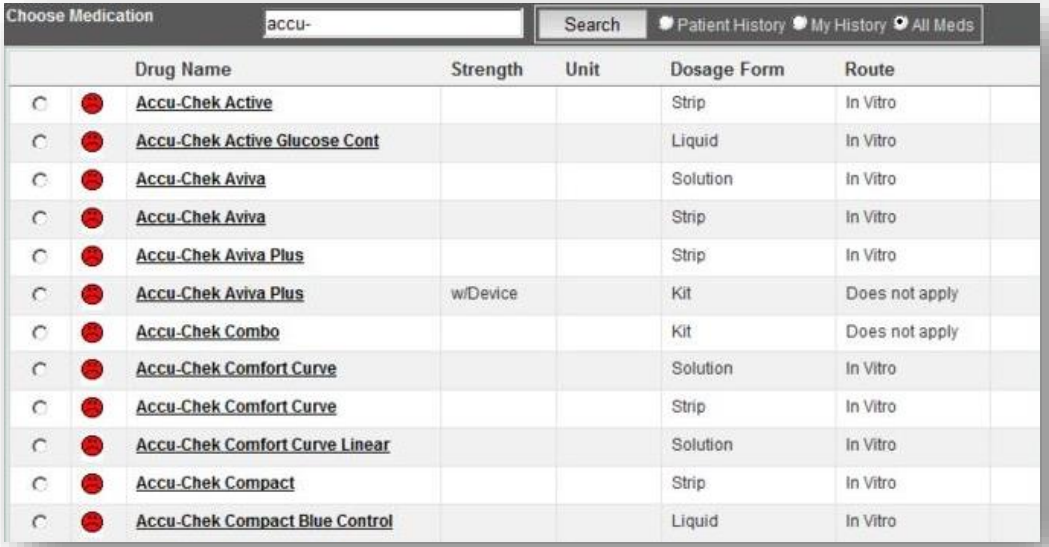
Biosimilar must be available in EHRs to be prescribed

Product Naming should consider how product will be listed in ePrescribing systems

- HCPs will need to be able to identify a biosimilar and easily distinguish it from the reference biologic
- EHR Vendors will need to clearly distinguish when a biosimilar is interchangeable

IDN order sets will need to be updated when existing biologic name change occurs

Access in EHR
HCPs need to easily identify and prescribe a biosimilar in the EHR



NCPDP Standards Work Around Electronic Communication of Biologic Substitution

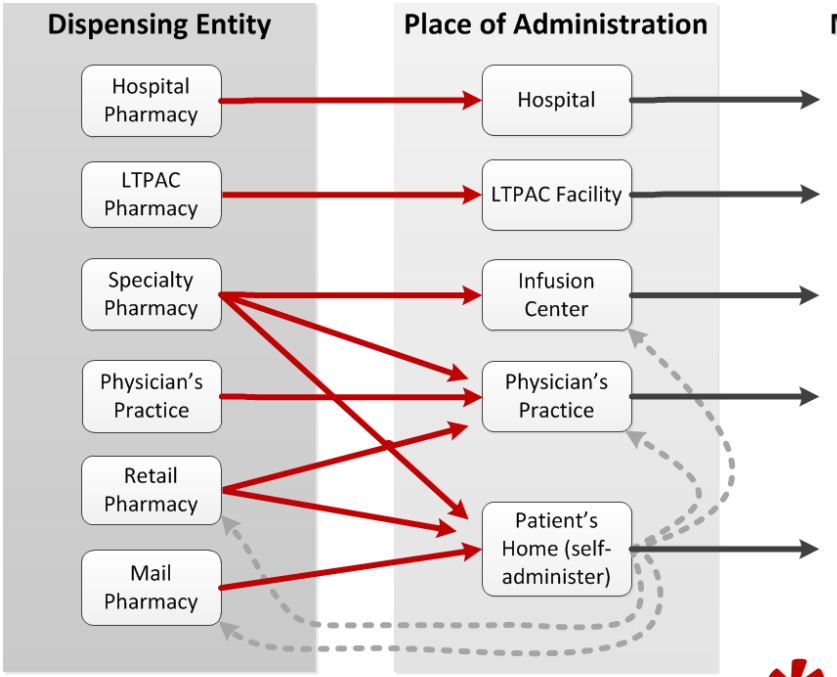
- NCPDP Biologics and Biosimilars Task Group Formed Sept, 2016
- **Goal:** Evaluate existing NCPDP standards including RxFill and Medication History (MedHx) on viability for use as electronic communications from pharmacy to provider for biologic and biosimilar substitution

National Council for Prescription Drug Programs

NCPDP

- **DERF passed at NCPDP meeting, May 2017**
- Will allow electronic communication of biologic and biosimilar substitution using RxFill
  - Adds a message type of "Biosimliar Substitution" to RxFill message type
  - Will allow providers to filter on and receive these types of RxFill messages only

Dispensing, Administration & Reporting Scenarios



Many Adverse Drug Event Reporting Scenarios

Reported by hospital staff or hospital pharmacy staff *

Detected by facility staff. Reported by facility or LTPAC pharmacy staff *

Detected during administration and reported by infusion center or specialty pharmacy staff *

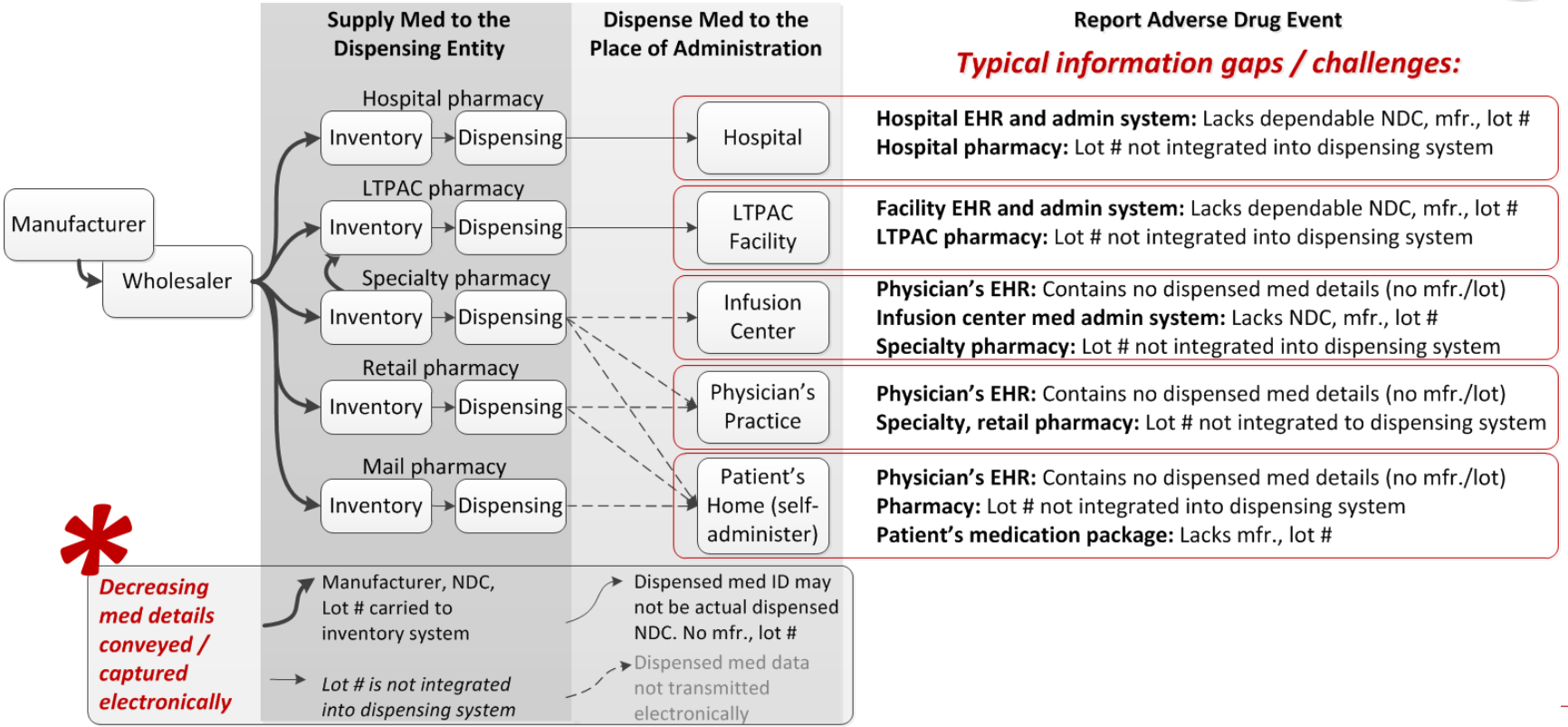
Detected during administration and reported by clinic staff *

Detected by patient and...
(a) self-reported
(b) discussed with and reported by clinic staff
(c) discussed with and reported by infusion center staff
(d) discussed with / reported by pharmacy staff

* ***OR… Adverse reaction is detected and reported later … by the patient or at subsequent provider visit***

ADE reporting occurs at different times and places. All systems need dispensed medication details

Importance of capturing product information for ADE reporting



Recommendations for working with IDNs

- Ensure product is being displayed accurately in EHR
  - New Names with suffix
  - Name changes
  - Interchangeability indicator
- Understand Federal and State Regulations surrounding biologics and biosimilars and ensure pharmacies have process in place for communication of substitution
- Understand IDNs ability to capture required product information for adverse event reporting

Questions

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